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(71) Applicant: BIOMEDTECH ENGINEERING, INC. [US/US]; 10521 West Forest Home Avenue, Hales Corners, WI 53130 (US).

(72) Inventor: OLSEN, David, J.; 10521 West Forest Home Avenue, Hales Corners, WI 53130 (US).

(74) Agents: KRYSHAK, Thad, F. et al.; Quarles & Brady, 411 East Wisconsin Avenue, Milwaukee, WI 53202 (US).

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(54) Title: METHOD FOR TREATMENT AND PREVENTION OF DISEASE IN ANIMALS

(57) Abstract

Methods of increasing the effective amount of growth hormone in an animal to stimulate the animal's immune system during the early stage of nocturnal sleep results in strengthening the animal's immunue sytem.

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METHOD FOR TREATMENT AND PREVENTION OF DISEASE IN ANIMALS

The present invention relates generally to the treatment and prevention of disease. More particularly, it relates to methods for strengthening the immune system of an animal, including a human.

Disease in animals is primarily overcome by the animal's immune system. It is known that growth hormone (also known as somatotropin) has a stimulative effect on the immune system. This is a result of its effect on T-cells, macrophages and other parts of the immune system.

It would be advantageous to have methods of increasing the production of growth hormone so that the stimulation of an animal's immune system is increased.

It is an object of the present invention to disclose methods of increasing the effective amount of growth hormone in an animal so that the stimulation of the animal's immune system is increased.

I have discovered that the immune system of an animal can be stimulated if the effective amount of growth hormone in the animal is increased during the early stage of nocturnal sleep (i.e. approximately the first 90 minutes).

More specifically, I have discovered that if during the early nocturnal sleep of an animal, such as a human, the effective amount of growth hormone in the animal is increased, the immune response of the animal is increased

and the production of T-cells, macrophages and other parts of the immune system are optimized to create an optimal immune response in the animal.

The effective amount of growth hormone may be increased by either administering to the animal substances that directly increase the growth hormone or by methods which block the adverse effects of melatonin on the animal's own growth hormone production.

Methods of directly increasing the amount of growth hormone include the following:

(1) By Growth Hormone Supplementation

In this embodiment of the method the levels of growth hormone in an animal are increased by administering growth hormone itself to the animal before the onset of the early stage of nocturnal sleep so that increased growth hormone is available during that early stage of nocturnal sleep.

(2) By Administering Growth Hormone Stimulating Chemicals

In this embodiment of the invention the effective amount of growth hormone in an animal is increased by administering to the animal a substance that stimulates growth hormone production in the body during the early stage of nocturnal sleep so that increased growth hormone is available during that early stage of nocturnal sleep.

The adverse effects of melatonin production on growth hormone production can be blocked until after the early stage of nocturnal sleep by one of the following embodiments of the methods of the present invention:

(1) By The Chemical Blocking Of The Production Of Melatonin

In this embodiment of the method the patient is administered a safe and effective amount of a substance that blocks the production of melatonin until after the early stages of nocturnal sleep (i.e., approximately the first 90 minutes of human sleep). The substance is given to the patient daily before sunset at a time sufficiently prior to sunset for the substance to be absorbed by the

body and to begin the blocking of the production of melatonin at about the time of sunset and to continue the blocking until the onset of sleep and during the early stage of nocturnal sleep.

(2) By The Use Of Light To Block The Production Of Melatonin.

In this embodiment of the method, the patient is exposed to a bright light (1,500 Lux to 12,000 Lux) for intermittent periods of time between the time of sunset and the onset of sleep every day in order to suppress production of melatonin by the pineal gland until after the onset of sleep.

In either of the above embodiments of the method, the adverse effects of melatonin on the production of growth hormone in an animal, such as a human, are blocked until after the early stage of nocturnal sleep so that the stimulation of the body's immune response to disease by growth hormone is increased. When melatonin production is suppressed or its effects offset by greater amounts of growth hormone during approximately the first 90 minutes of sleep, the animal's immune response to disease is optimized.

Description of the Preferred Embodiments

In the preferred embodiments of the method of the present invention, the effective amount of growth hormone in the animal's body during the early stage of nocturnal sleep is increased by blocking the adverse effects of melatonin on growth hormone production by either the administration of a safe and effective amount of a substance or by the exposure of the animal to bright light for an effective period of time.

Although a variety of substances can be used to block the adverse effects of melatonin, the presently preferred substances are beta-adrenergic antagonists. These substances are believed to act by blocking receptors in the pineal gland from receiving neural signals from the eyes. By blocking these neural signals the beta-adrenergic antagonists prevent the synthesis of

melatonin in the pineal gland.

Representative of the beta-adrenergic antagonists which can be used are propranolol hydrochloride and atenolol. Both of these products can be administered orally about one to seven hours prior to the onset of nocturnal sleep. Atenolol is administered in oral dosages of from 0.1 mg to 50 mg. The oral dosage for propranolol is from 0.1 mg to 60 mg.

The production of melatonin is believed to be suppressed by the beta-adrenergic blockers for sufficient time to allow optimal production of growth hormone in the pituitary gland. As a result, the optimal production of growth hormone yields optimum stimulation of the immune system resulting in optimal immune response.

Another type of compound that can be used to block the adverse effects of melatonin is N-acetyltryptamine 2-benzyl-N-acetyltryptamine (Luzindole). It is believed to suppress melatonin by antagonizing melatonin receptors in the body. By antagonizing these receptors, the compound prevents melatonin from acting on the pituitary gland and thus preventing melatonin's suppression of growth hormone. The oral dosage for Luzindole is 200 mg to 1000 mg.

Other substances that block the adverse effects of melatonin can also be used. For example, estradiol and progesterone have also been shown to suppress melatonin in the body.

The administration of a substance that blocks the adverse effects of melatonin is continued every day before sunset. The treatment is continued until all evidence of the disease is gone from the body.

In another preferred embodiment of the method of the present invention the adverse effects of melatonin in the animal are blocked by exposing the animal to a bright light (1,500 Lux to about 12,000 Lux) for effective intermittent periods of time from sunset to the onset of the early stage of nocturnal sleep to optimize the production of growth hormone resulting in optimal immune

response.

In the preferred embodiment of the method of the invention in which the effective amount of growth hormone in the animal's body is directly increased, growth hormone is administered to the animal shortly before the onset of the first stage of nocturnal sleep.

The growth hormone is administered orally in dosages of 1 mg to 20 mg before the onset of sleep each day so that it is absorbed by the body within 30 to 60 minutes after the onset of sleep.

The growth hormone supplements the body's own production of growth hormone during the first stage of nocturnal sleep when the pituitary gland is producing the greatest quantity of the hormone. The presence of the supplemental growth hormone increases the total growth hormone level above the normal level produced by the body, thus resulting in an increased stimulation of the immune response.

In still another embodiment, the effective amount of growth hormone is increased by administering to the animal a substance that stimulates growth hormone production during the early stage of nocturnal sleep. Representative of such substances are growth hormone releasing factor and analogs of growth hormone releasing factor. Growth hormone releasing factor is administered orally before the onset of sleep every day in dosages of 0.1 mg to 100 mg.

The growth hormone production stimulating substance is given to the patient shortly before the onset of sleep each day. The substance is given at a time that will allow the body to absorb it and synthesize additional growth hormone within approximately 30 to 60 minutes of the onset of sleep.

The growth hormone stimulating substance may act by offsetting the adverse effects of melatonin on growth hormone production. The substance can also be used to raise the growth hormone level above the level normally produced in the body. Optimal production of growth

hormone can then be achieved during approximately the first 90 minutes of sleep each day. This results in optimal stimulation of the immune system and optimal immune response.

With any of the above described embodiments of the method of the present invention, additional measures can be taken to help optimize the immune response in the animal:

(1) The patient can be instructed not to nap. This will result in making the onset of sleep come more easily and quickly when the patient goes to bed.

(2) The patient can be instructed not to eat or drink anything (except water) for several hours before going to bed. Sugar has been shown to suppress growth hormone. By not eating or drinking for several hours, all sugar in the body will be metabolized before the onset of sleep.

(3) The patient can be taken off all medications that have a suppressant effect on growth hormone or the immune system.

(4) The patient can be taken off all medication during the treatment. There may be some unknown suppressant effects of the medications the patient is taking. These could prevent optimizing the intended immune response.

(5) The patient can be given vitamin supplements. Studies have shown that some vitamins may help stimulate immune response.

(6) The patient can be instructed to go to bed at the same time every night. This in combination with the suppression of melatonin can help entrain the body to delay melatonin production until after the onset of sleep.

The methods described with or without the additional measures can be continued beyond the time disease is gone from the body. By extending the treatment, the immune response may be improved to prevent future recurrences of the disease. The methods also can be combined with one

or more of the other described treatment procedures to increase immune response.

It will be apparent to those skilled in the art that the method of the present invention can also be used to strengthen the body's immune response to prevent the occurrence of disease.

Example 1

A white, male patient, age 20, is exposed to the bright light (10,000 Lux) of a light fixture (Natural Illuminator 10,000 Model) from the Hughes Lighting Technologics Company for intermittent periods of time (of about 15 minutes to 60 minutes each) between sunset and the onset of sleep each night for 30 days. At the end of that time an analysis shows that the patient's immune system has been stimulated.

It will be apparent to those skilled in the art that a number of modifications and changes can be made without departing from the spirit and scope of the invention. Therefore, it is intended that the invention only be limited by the claims.

Claims

1. A method for strengthening the immune system of an animal needing immune system strengthening which comprises increasing the effective amount of growth hormone in such an animal during the early stage of nocturnal sleep.

2. A method of claim 1 in which the effective amount of growth hormone is increased by administering to the animal a substance that suppresses the adverse effects of melatonin on growth hormone in the animal.

3. A method of claim 2 in which the substance is a beta-adrenergic antagonist.

4. A method of claim 1 in which the effective amount of growth hormone is increased by administering to the animal growth hormone.

5. A method of claim 1 in which the effective amount of growth hormone is increased by administering to the animal a chemical substance that stimulates the increased production of growth hormone in the body.

6. A method of claim 1 in which the effective amount of growth hormone in an animal is increased by blocking the adverse effects of melatonin on growth hormone production by exposing the animal to a safe and effective amount of visible light.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/14839

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 38/27
US CL : 514/2, 21

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/2, 21

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN, APS
search terms: growth hormone or somatotropin and immun?(5a)stimulat?

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,837,202 (EDWARDS, III ET AL.) 06 June 1989, see the entire document.	1,4,5
Y	Acta Endocrinologica (Copenh), Volume 123, issued 1990, P. Franco et al., "Influence of growth hormone on the immunosuppressive effect of prednisolone in mice", pages 339-344, see the entire document.	1,4,5
Y	Clin. exp. Immunol., Volume 68, issued 1987, B. Lawler Goff et al., "Growth hormone treatment stimulates thymulin production in aged dogs", pages 580-587, see the entire document.	1,4,5

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Date of the actual completion of the international search 27 MARCH 1995	Date of mailing of the international search report 18 APR 1995
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JEAN C. WITZ Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/14839

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Science, Volume 239, issued 12 February 1988, C. Edwards et al., "A Newly Defined Property of Somatotropin: Priming of Macrophages for Production of Superoxide Anion", pages 769-771, see the entire document.	1,4, 5
Y	Progress in NeuroEndocrinImmunology, Volume 3, Number 4, issued 1990, D. Weigent et al., "Growth Hormone and the Immune System", pages 231-241, see the entire document.	1,4,5
Y	Biochemical Pharmacology, Volume 38, Number 5, issued 01 March 1989, K. Kelley, "Growth Hormone, Lymphocytes and Macrophages", pages 705-713, see the entire document.	1,4,5
Y	WO, A, 93/00109, (CARLSSON ET AL.) 07 January 1993, see the entire document.	1,4,5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/14839

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 4, 5

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/14839

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows:

A method of strengthening the immune system by
1)administering growth hormone/growth hormone stimulating substances;
2)administering a substance that suppresses melatonin/a beta-adrenergic antagonist;
3)administering light.

The claims are deemed to correspond to the species listed above in the following manner:

1)Claims 1, 4, 5
2)Claims 2, 3
3)Claim 6

The following claims are generic: none

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical featuresfor the following reasons: The substances administereddiffer in source, chemical composition and mode of administration.